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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,972	02/14/2002	Richard J. Whitley	UAB-16102/22	5479

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/009,972	Whitley et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-15 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on Feb 14, 2002 is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The filing papers included an amendment filed for PCT/US00/40165 under PCT Rules 66.3 and 66.8. The paper is noted; however, the amendment contained therein was not filed as an amendment to the instant claims, the amendment has not been entered into the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).
>
> The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The first sentence of the specification contains no reference to the provisional applications; no application data sheet has been filed. The inventions described in provisional applications 60/138,173 and 60/144,314 are significantly narrower than the instant invention. These applications describe specific neuroattenuated, replication competent HSV-1 having both copies of the γ34.5 gene replaced with an expression construct consisting of an Egr-1 promoter and poly

A sequence operably linked to coding sequence for: 1) the p40 and p35 subunits of IL-12 separated by an IRES ('173); 2) GM-CSF ('173); or 3) *E. coli* cytosine deaminase ('314), and no other genetic alterations to the HSV-1 genome. None of the instant claims is limited to one or more of the specific recombinant HSV-1 described in the provisional applications. The instant claims are directed to a significantly broader invention which was not described in the '314 or '174 applications. The instant claims place no limits on HSV sequences retained or deleted, on the promoter linked to the IL-12, GM-CSF, or CD coding sequence, on the type of HSV, or whether the HSV is replication competent or deficient or restricted. Consequently, the claimed invention does not meet the written description requirement for obtaining benefit of priority.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text. The cover sheet of the WO document does not meet this requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-5, 9-11, and 13-15 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Wechsler et al. US 2002/0098170.

Wechsler teaches a pharmaceutical composition comprising substantially aneurovirulent replication-competent HSV-1 whose genome comprises deletion of both copies of the γ34.5 gene and LAT coding sequence and a nucleic acid sequence encoding IL-12 or GM-CSF operably linked to a LAT promoter. Wechsler also teaches a method for treating cancer in a subject by administering a therapeutically effective amount of the HSV directly to the tumor by injection. See entire reference, especially paragraphs 0024, 0025, 0040, 0044, 0045, 0054-0057, and 0067.

Claims 9, 10 and 15 are rejected under 35 U.S.C. 102(a), (b) & (e) as being clearly anticipated by DeLuca, US 5,804,413.

DeLuca discloses an substantially, aneurovirulent HSV comprising an expression construct encoding cytosine deaminase. Recitation of "pharmaceutical" in the instant claims indicates the intended use for the HSV vector, but imparts no material limitation that would distinguish the claimed composition from one used to transfect cultured cells. See especially col. 5, lines 43-60, and claim 34. Limiting claim 9 to replication competent HSV vectors would overcome this rejection.

Claims 1, 2, 4, 9, 11, and 15 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Boursnell et al., US 6,287,557.

See col. 20, line 7 to col. 22, line 37, and claims 1-5. Inasmuch as loss of the gH gene (replaced by the GM-CSF gene) in the HSV results in the production of non-infectious particles, the virus is replication competent.

Claims 1, 2, 4, 9, 11, and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Inglis et al., WO 96/26267.

Inglis discloses a method for treating a subject with cancer comprising administering to the subject an HSV-1 or HSV-2 which has a GM-CSF coding sequence in place of the gH, gD, gL, ICP4, ICP8 or ICP27 coding sequence. The HSV may be injected into a tumor. Inasmuch as loss of the gH gene (replaced by the GM-CSF gene) in the HSV results in the production of non-infectious particles, the virus is replication competent. See page 16, lines 17-20; pages 28-31.

Claims 1, 2, 4, 9, 11, and 15 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Todryk et al. (Hum. Gene Ther. 10 (17): 2757-2768, 20 Nov. 1999).

Todryk discloses a method for treating a subject with cancer comprising injecting into a tumor an HSV-2 which has a GM-CSF transgene in place of the gH gene. Inasmuch as loss of the gH gene (replaced by the GM-CSF gene) in the HSV results in the production of non-infectious particles, the virus is replication competent. See page 2762, col. 2 to page 2763, col. 1.

Claims 1-3, 9, 10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Toda et al. (J. Immunol. 160 (9): 4457-4464, May 1998).

Toda discloses a pharmaceutical composition comprising replication competent HSV-1 helper virus and a replication-defective HSV-1 which comprises multiple copies of an expression construct wherein a CMV promoter is operatively linked to coding sequences for the p40 and p35 subunits of IL-12 separated by an IRES. Toda also discloses a method of treating cancer in a subject with the composition by injecting it into a tumor. See page 4459, col. 2 to page 4461, col. 2. The replication-defective HSV-1 is aneurovirulent, since it will not replicate or produce toxic HSV proteins in infected neurons (or any other cell).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wechsler et al. US 2002/0098170 in view of Toda et al. (J. Immunol. 160 (9): 4457-4464, 1 May 1998).

Wechsler has been described above, while it describes an HSV-1 which expresses IL-12 under control of the LAT promoter, it does not disclose the structure of the transcription unit for doing so.

However, Toda et al. discloses that it was well known that IL-12 is a heterodimer, and describes a construct for expressing IL-12 from an HSV vector. The construct comprises the coding sequence for the IL-12 p40 subunit followed by an IRES and then by coding sequence for the IL-12 p35 subunit.

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have constructed the HSV-1 of Wechsler which expressed IL-12 under control of the LAT promoter utilize the construct as taught by Toda, since this expression construction had been taught for expression of IL-12 from a HSV vector.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andreansky et al. (Gene Therapy 5 (1): 121-130, Jan. 1998) in view of Toda et al. (J. Immunol. 160 (9): 4457-4464, 1 May 1998).

Andreansky discloses a general method for treating cancer (e.g. glioma) which involves intratumoral injection of a pharmaceutical composition containing a cytotoxic aneurovirulent, replication-competent HSV-1. The HSV-1 is deleted for both copies of the γ34.5 gene, and in their place contains a coding sequence for a cytokine under control of an Egr-1 promoter to enhance tumor destruction. The cytokines chosen for the study to test this idea were IL-4 (anti-tumor) and IL-10 (immunosuppressive). The HSV-1 which expressed IL-4 was found to improve survival of the subjects as compared to those treated with HSV-1 lacking the γ34.5 gene (but without a cytokine transgene) or HSV-1 expressing IL-10. The treatment with the HSV-1 expressing IL-4 was palliative. The authors suggest that other genes which would alter the immune response to tumor cells could be used. See entire document, especially pages 126-127. Andreansky does not teach using an IL-12 transgene in their method.

However, Toda discloses a similar method but combining a cytotoxic, aneurovirulent, replication-competent HSV-1 deleted for both copies of the γ34.5 gene and a replication defective HSV vector comprising an IL-12 expression cassette. The IL-12 expression cassette comprised a promoter operatively linked to coding regions for the two IL-12 subunits separated by an IRES. Toda disclosed that the combination enhanced the anti-tumor efficacy of the cytotoxic HSV-1 by local IL-12-mediated induction of tumor specific cytotoxic T-lymphocyte

activity and IFN-γ production leading to increased tumor necrosis. See Fig. 1 and pages 4462-4463.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have substituted an IL-12 expression construct for the IL-4 expression construct in the HSV-1 of the method taught by Andreansky, since Andreansky suggested that other genes encoding other immune modulating could be used, and Toda taught in a similar system that IL-12 expression in combination with a cytotoxic replication-competent HSV-1 enhanced the antitumor activity of the HSV-1.

Drawings

New formal drawings are required in this application for the reasons set forth on the attached PTO-948. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The corrected drawings should be filed as a separate letter to the draftsperson, MPEP 608.02(r). The objection to the drawings will not be held in abeyance.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The

faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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